National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Sanofi (company)	We feel it is appropriate to evaluate this topic and agree with the Single Technology appraisal route proposed.	Thank you for your comment. No action required.
	Association of British Clinical Diabetologists	Evaluating this therapy through a single technology appraisal appears entirely appropriate.	Thank you for your comment. No action required.
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	We recommend that this is a highly specialised technology evaluation.	Thank you for your comment. This appraisal does not meet the criteria for a highly specialised technologies evaluation. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Diabetes UK	Yes – we consider this appropriate and timely – though need to be clear on process and timing for MHRA assessment. Yes to STA process.	Thank you for your comment. No action required.
	Juvenile Diabetes Research Foundation (JDRF)	JDRF believes it is very appropriate for NICE to evaluate this topic using the evaluation route proposed.	Thank you for your comment. No action required.
Wording	Sanofi (company)	We believe that the definition of the population in the draft scope as “people aged 8 and over at risk of developing type 1 diabetes” is entirely disparate from the patient population in which teplizumab has been investigated. In accordance with the US FDA approved indication (1) and clinical trial inclusion criteria (2) it would be more appropriate to consider in the scope people who are already diagnosed with type 1 diabetes (T1D) that is at Stage 2. This patient population has been defined in the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines, according to which people with Stage 2 T1D have pre-symptomatic disease, characterised by multiple islet autoantibodies and abnormal glucose tolerance (3). This is distinct from Stage 1 and Stage 3 of the disease (3). Teplizumab does not currently have a marketing authorisation in the UK, however we propose the following wording is used, in line with the FDA approved indication (1) and clinical trial inclusion criteria (2) “delaying the onset of Stage 3 Type 1 diabetes (T1D) in adults and paediatric patients aged 8 years and older with Stage 2 T1D”.	Thank you for your comment. The title and remit have been updated to better reflect the patient population

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	No – suggest changing to: To appraise…for delaying the onset of Stage 3 type 1 diabetes in people aged 8 and over **with early-stage type 1 diabetes with dysglycaemia (stage 2) to prevent them progressing to insulin therapy.** Note this was the FDA licensing approval. Individuals with a single antibody are 'at risk', but those with 2 or more islet autoantibodies have early stage T1D. But it is only those in stage 2 (dysglycaemia) where teplizumab has been approved in the U.S. by the FDA.	Thank you for your comment. The title and remit have been updated to better reflect the patient population
	Diabetes UK	Yes	Thank you for your comment. No action required.
	Juvenile Diabetes Research Foundation (JDRF)	Yes, it does.	Thank you for your comment. No action required.
Additional comments on the draft remit	Sanofi (company)	**Request for Scoping Workshop** Given the draft remit has not identified the population correctly, we believe that a scoping workshop is critical. Such a workshop could help to avoid issues and complexity during the appraisal and potentially lead to faster access for patients.	Thank you for your comment. A scoping workshop was conducted, and responses have been included in the scope

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Clinical Diabetologists	Screen detected type 1 diabetes is increasing. The ELSA study has identified 90 children with pre-T1D over the past 2 years, many of whom will be eligible for teplizumab therapy. If teplizumab delays the need for insulin by about 3 years in each of these children, this is almost 270 years of insulin treatment that the NHS will not need to cover. The UK needs to be able to offer this therapy to its patients.	Thank you for your comment. No action required.
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	• Distinguish 'risk' from 'disease'. • Specify the exact remit of teplizumab – presumably only stage 2 type 1 diabetes with dysglycaemia i.e. 2 or more islet autoantibodies with dysglycaemia. • State how islet autoantibody and dysglycaemia status is confirmed	Thank you for your comment. The title, remit and body of the scope have been changed to better reflect the relevant patient population. Information about how autoantibodies and dysglycaemia are detected has also been added.
	Diabetes UK	Consideration should be given to separately assessing use in children aged 8-18 years where cost effectiveness may be greater due to reduced exposure to hyperglycaemia in early life and throughout life. It would be less expensive to identify (by screening) eligible individuals from high risk groups e.g. first degree relatives than the whole population.	Thank you for your comment. If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities

Section	Consultee/ Commentator	Comments [sic]	Action
			implications of its considerations.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sanofi (company)	The document appears to predominantly focus on symptomatic T1D and does not refer to stages associated with the disease. T1D staging is crucial for the definition of the patient population eligible for treatment with teplizumab, based on the approved FDA indication (1) and clinical trial inclusion criteria (2). We suggest that the following wording is included: "T1D progresses across the following three stages (3-9): • **Stage 1 T1D**, the presence of ≥2 pancreatic islet autoantibodies indicates that the autoimmune attack and β-cell loss has begun, but people with Stage 1 T1D have a normal concentration of blood glucose. Clinical symptoms are not present at Stage 1. The risk of progression of Stage 1 to Stage 2 T1D is currently not well understood, however there is up to a 44% 5-year and 80-90% 15-year risk of paediatric patients progressing to Stage 3 T1D from Stage 1 T1D. • **Stage 2 T1D**, continued autoimmune attack by autoreactive T cells causes further β-cell loss. Stage 2 T1D is defined as ≥2 pancreatic islet autoantibodies and dysglycaemia (abnormalities in blood glucose levels) without overt hyperglycaemia. Clinical symptoms are not present at Stage 2. There is up to a 75% 5-year	Thank you for your comment. Information has been added to explain the stages of type 1 diabetes. The source of incidence statistics have been changed to better represent England and Wales.

Section	Consultee/ Commentator	Comments [sic]	Action
		risk of paediatric patients progressing to Stage 3 T1D from Stage 2 T1D which approaches 100% for lifetime risk. • **Stage 3 (symptomatic) T1D**, is defined by overt hyperglycaemia, accompanied by clinical symptoms. It is in Stage 3 that people with T1D will usually require lifelong exogenous insulin therapy as treatment. This is currently when most people with T1D are typically diagnosed. Some literature also refers to Stage 4 T1D in reference to established disease, however this terminology is not currently widely used in routine clinical practice." The second paragraph states "Type 1 diabetes can present at any age, with peaks in presentation between ages 5 to 7 and around puberty", citing Los and Wilt (2023) as the source of the data. Although this may reflect the global trends, data from the NHS National Diabetes Audit (NDA) indicates that the peak in the UK is around 12 years of age (10). We feel it would be more accurate to cite the NDA data given these are UK-specific. Furthermore, only patient numbers for Stage 3 T1D are stated, however given this appraisal is for Stage 2 T1D we feel reference to Stage 2 T1D should be made. We suggest the following wording is added: "The epidemiology of Stage 2 T1D is uncertain in England given that there are no general population screening programmes for presymptomatic T1D in the UK (11) and there is uncertainty regarding the typical duration of Stage 2. The number of people diagnosed with Stage 2 T1D in England is expected to be low with most people with T1D in the UK currently diagnosed at Stage 3.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Some individuals in the UK may be diagnosed with presymptomatic (Stage 1 or Stage 2) T1D as part of various studies, such as clinical trials and observational studies (e.g., ELSA in children, T1DRA in adults), including those which are conducted specifically in individuals with a first-degree relative with Stage 3 T1D (e.g., INNODIA; 11-12)" In paragraph three, NICE's clinical guidelines on the diagnosis and management of type 1 diabetes in adults (NG17) are referenced, however these guidelines are for the treatment of Stage 3 T1D only. In the context of teplizumab, the consensus guideline initiated by Breakthrough T1D (formerly JDRF) and endorsed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (13) and the ISPAD consensus guideline (3) covering Stage 2 disease would be more appropriate sources. Similarly, the draft scope refers to treatment with metformin and sotagliflozin with insulin which are both treatments for Stage 3 T1D. Although it may be appropriate to reference these in relation to subsequent treatment once people progress to Stage 3 T1D, we feel the document lacks information on the management of Stage 2 T1D. Although there is no existing treatment pathway, interventions such as monitoring, education and psychosocial support have been recommended (13) and we believe including the information relevant to Stage 2 T1D in the background is crucial to ensure the scope of the appraisal is appropriately defined.	
	Association of British Clinical Diabetologists	No concerns with accuracy. For completeness, please consider including current marketing authorisation in the US	Thank you for your comment. Marketing authorisations from other countries are not usually included in NICE scopes. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	The Background. Paragraph 4 – include discussion about NICE clinical type 1 diabetes guideline in children. Paragraph 6 – see comments above - remove 'risk'.	Thank you for your comment. Information about NG18 has been added to the background, References to 'risk' have been removed
	Diabetes UK	Clarity needed in paragraph 2 which sets out numbers of diagnosed type 1 E&W – the figure here describes **newly diagnosed** (incidence) - this should be specified. Also data now available for 2022-3? We avoid the term "control" as people with diabetes report feeling judged by such language. We prefer "management" – please could you consider using this. For reference we have linked to the 'Language Matters' guide developed by NHS England and supported by Diabetes UK and other patient and healthcare professional representatives: https://www.diabetes.org.uk/resources-s3/2018-09/language-matters_language%20and%20diabetes.pdf. The summary of NICE's recommendations and guidance for treatment of type 1 diabetes is incomplete as it misses recommendations on pump treatment (CSII) for some people, as in TA151. And Hybrid closed loop for some people (including all children and young people under 18 years old) as in TA943	Thank you for your comment. The incidence rate has been clarified. Incidence data for the 2022-23 financial year is not yet available. We have referred to dietary management rather than dietary control but have kept hypoglycaemia control and control of cardiovascular risk to align with NG17 which is being referred to. We have reduced the discussion around treatment for stage 3

Section	Consultee/ Commentator	Comments [sic]	Action
			diabetes in the background section generally.
	Juvenile Diabetes Research Foundation (JDRF)	JDRF recommends including information about the four stages of type 1 diabetes in this section, considering teplizumab, if approved, will be used at stage 2.	Thank you for your comment. Information has been added to explain the stages of type 1 diabetes.
Population	Sanofi (company)	We believe that the definition of the population in the draft scope as “people aged 8 and over at risk of developing type 1 diabetes” is entirely disparate from the patient population in which teplizumab has been investigated. In accordance with the FDA approved indication (1) and clinical trial inclusion criteria (2) it would be more appropriate to consider in the scope people who are already diagnosed with type 1 diabetes (T1D) that is at Stage 2. This patient population has been defined in the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines, according to which people with Stage 2 T1D have pre-symptomatic disease, characterised by multiple islet autoantibodies and abnormal glucose tolerance (3). This is distinct from Stage 1 and Stage 3 of the disease (3). Teplizumab does not currently have a marketing authorisation in the UK, however we propose the following wording is used, in line with the FDA approved indication (1) and clinical trial inclusion criteria (2) “delaying the onset of Stage 3 Type 1 diabetes (T1D) in adults and paediatric patients aged 8 years and older with Stage 2 T1D”.	Thank you for your comment. The population has been updated in line with suggestions from consultation and the scoping workshop

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Clinical Diabetologists	Please consider a clearer definition of 'risk of developing T1D'. We would suggest stating this indicates multiple islet antibody positivity with dysglycaemia.	Thank you for your comment. The population has been updated in line with suggestions from consultation and the scoping workshop
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	No – see above – this should be those aged 8 years and above in stage 2 type 1 diabetes i.e. 2 or more islet autoantibodies with dysglycaemia (state definitions of both)	Thank you for your comment. The population has been updated in line with suggestions from consultation and the scoping workshop
	Diabetes UK	Yes, though see note above about potential added benefits in 8-18 years. Also the term "at risk of developing type 1 diabetes" may be confusing. It refers to the development of an advanced stage of insulin making cell loss that requires exogenous insulin therapy. All the individuals treated would have/will develop type 1 diabetes to this advanced stage. The term "at risk" suggests that some may never develop it and be treated unnecessarily, which is may be misleading	Thank you for your comment. The population has been updated in line with suggestions from consultation and the scoping workshop
	Juvenile Diabetes Research	JDRF recommends rewording "people aged 8 and over at risk of developing type 1 diabetes" to "people aged 8 and over in the early stages of type 1 diabetes" OR "in stage 2 of type 1 diabetes"	Thank you for your comment. The population has been updated in line with suggestions from

Section	Consultee/ Commentator	Comments [sic]	Action
	Foundation (JDRF)		consultation and the scoping workshop
Subgroups	Sanofi (company)	Given the small number of people diagnosed with Stage 2 T1D and the lack of meaningful evidence on patient subgroups, we believe the entire eligible patient population should be considered.	Thank you for your comment. If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.
	Association of British Clinical Diabetologists	No groups need separate consideration.	Thank you for your comment. If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	Yes – see above; stage 2 type 1 diabetes and aged 8 years and over. Children could be considered separately as delaying clinical type 1 diabetes could be anticipated to have a larger effect in children compared to adults, because: 1) children are exposed to longer duration of hyperglycaemia and are therefore at a higher risk of ensuing diabetes health-related complications and reduced life expectancy 2) children are reliant on parents/carers/school leaders for their diabetes management, which also translates to time lost from work by parents/carers, and time lost form education for 3-monthly hospital clinic appointments/unscheduled hospital contacts. 3) children have destabilisation in diabetes control as they go through growth and puberty. NICE could consider a further sub analysis of screening, follow up and teplizumab administration in first degree relatives (FDRs), who have a 15 times higher risk of developing T1D. However this only represents 10-15% of the type 1 diabetes population but would be easier (and more cost effective) to identify because: 1) the index cases are seen in routine clinics, and 2)FDRs have prior knowledge of the burden of living with T1D and may be more likely to take up the offer of intervention to delay T1D onset.	Thank you for your comment. If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.
	Diabetes UK	Again, children 8-18 years may be considered separately as may be more cost effective in this age group as 1) children especially under the age of 12 progress more rapidly to losing insulin production and needing insulin treatment (2) individuals who begin their diabetes journey in childhood have	Thank you for your comment. If evidence allows, consideration

Section	Consultee/ Commentator	Comments [sic]	Action
		more years of glycaemic exposure and are therefore at increased risk of developing complications earlier with more life years lost. Teplizumabs delays the age at which significant hyperglycaemia begins. We had some feedback from parents of children in the ELSA screening study – this is what they have said: A parent who responded picked up on the benefits of offering it to younger children less able to self-manage independently: ***"I think the younger the child, the more benefit for the individual and families of the individual. It can be a really difficult condition to manage, so I believe any delay will help a child to improve the quality of life of their childhood."*** Other parents also raised the importance of big transitional periods in childhood, such as moving from primary school to secondary school and becoming a teenager: ***"My daughter is currently 10 years old. She has one more year at primary school and will then be transitioning to high school. She will be facing a lot of changes in her life and I think if we could delay the onset of Type 1 diabetes until she is a bit older, she will be more emotionally mature to deal with the situation."*** ***"Teenage years are especially difficult, for kids and parents, so delaying the onset would help us reach a stage of maturity where my child is more sensible and I am not seen as the imposing parent"***	may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.

Section	Consultee/ Commentator	Comments [sic]	Action
		"If a treatment was made available to delay type 1 in my child it would allow her to get through some of her teen years which are already challenging enough without the burden of type 1." In addition, others noted that having other conditions – one child has ADHD for example – can also make coming to terms and managing diabetes more difficult: ***"[…]my child has ADHD, which means they have difficult controlling impulses and having routines, 2 essential things when dealing with diabetes"***	
	Juvenile Diabetes Research Foundation (JDRF)	No.	Thank you for your comment. If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.
Comparators	Sanofi (company)	We are concerned that "no prophylaxis" has been used as the comparator, as this infers that teplizumab is a prophylactic treatment. Teplizumab can be considered a disease-modifying immunotherapy but is not prophylactic.	Thank you for your comment. The comparators section has been updated to refer to established clinical management

Section	Consultee/ Commentator	Comments [sic]	Action
		A more appropriate wording would be “best supportive care” which would include monitoring, education on diabetes care and psychosocial support (13). The provision of these services is not currently standardised and there are currently no UK-specific guidelines for the management of people with Stage 2 T1D.	with examples of what this may include.
	Association of British Clinical Diabetologists	No concerns – there are no current comparators.	Thank you for your comment. The comparators section has been updated to refer to established clinical management with examples of what this may include.
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	No – this should be ‘no treatment’	Thank you for your comment. The comparators section has been updated to refer to established clinical management with examples of what this may include.
	Diabetes UK	Yes – there are no existing comparators for pre-type1 drug therapy to delay type 1 diabetes.	Thank you for your comment. The comparators section has been updated to refer to established clinical management

Section	Consultee/ Commentator	Comments [sic]	Action
		No prophylaxis supplemented with education, watching and waiting, alongside blood glucose monitoring (CGM) is only other course currently to aid a “softer landing” (easier onset /diagnosis experience).	with examples of what this may include.
Outcomes	Sanofi (company)	In line with the comments above on the incorrectly defined population, we believe the outcomes are not appropriate to Stage 2 T1D. We propose removing the following, as these are not relevant to patients already diagnosed with T1D: • rate of new diabetes per year • time to diabetes diagnosis We suggest adding the following: • **Time to progression from Stage 2 to Stage 3 T1D** in line with the patient population and also the primary endpoint of the pivotal TN-10 trial (14). • **Rate of progression from Stage 2 to Stage 3 per year** in line with the patient population and an important endpoint in the TN-10 trial (14). • **Levels of stimulated C-peptide** which is a measure of endogenous insulin secretion in patients and thus reflects preservation of the function of the beta-cell in the pancreas which are responsible for insulin production and release (15-16). This is an important indicator of disease modification in delaying the onset of Stage 3 T1D and was also a secondary endpoint in the TN-10 clinical trial (14). • **Impact on the patient.** Stage 3 T1D is known to have an impact on the patient including time spent managing the condition (17), time spent off school (18) and distress in the workplace (19). Given teplizumab is expected to delay the onset of Stage 3 T1D in people	Thank you for your comment. The outcomes section has been updated in line with suggestions from consultation and the scoping workshop

Section	Consultee/ Commentator	Comments [sic]	Action
		with Stage 2 T1D, it is important that the potential benefit of delaying these impacts are captured. • **Impact on caregiver.** T1D is known to have an impact on caregivers, for example, through burden of care, financial implications, and sense of vigilance (20). Given the anticipated marketing authorisation includes children above the age of 8, it is important this outcome is included. We agree with the inclusion of mortality, adverse effects of treatment and health-related quality of life	
	Association of British Clinical Diabetologists	The C peptide preservation associated with Tzield would be expected to reduce the long-term complications associated with T1D. If the event horizon for cost effectiveness analysis is sufficiently long-term, this benefit of a reduction in complications should be detectable. Therefore, it would be worth considering the additional outcomes of diabetes related complications (kidney failure, eye disease etc). Not clear why mortality is included. There is a reduction in emergency presentation with diabetic ketoacidosis (DKA) and hence in DKA associated mortality when patients are screened for T1D and when this condition is picked up early, but this is a benefit of screening and not of Tzield.	Thank you for your comment. The outcomes section has been updated in line with suggestions from consultation and the scoping workshop
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	No – Second bullet point should read: Time to starting insulin treatment Should also include other PROMS, specifically around psychological outcomes related to knowing the impact of a positive screen test e.g.	Thank you for your comment. The outcomes section has been updated in line with suggestions from

Section	Consultee/ Commentator	Comments [sic]	Action
		measures of anxiety and depression, as this treatment will only be given to those identified by screening and early identification of disease, e.g.2 parental time off work due to treatment vs attending clinic appointments/unscheduled hospital contacts. Uptake of screening (more people may come forward if treatments are available). Incidence of DKA at point of developing stage 3 type 1 diabetes Incidence of severe DKA at point of developing stage 3 type 1 diabetes Hospitalisation (and days on intensive care/high dependency) – related to having to screen to identify these children, and as a result, a reduction in the need for urgent hospital stay to start insulin/DKA.	consultation and the scoping workshop
	Diabetes UK	May also consider reduction in duration of exposure to blood glucose levels that put a person at risk of microvascular complications ie HbA1c > 6.5% = 48mmol/mol. Also should consider including psychological impact. Feedback we received from parents who participated in the ELSA study detailed the myriad significant quality of life benefits that their child and family could get if the treatment was approved and available. A common theme that stood out was the trauma and anxiety of a T1 diagnosis on child and parent and how that can be managed and mitigated following screening:	Thank you for your comment. The outcomes section has been updated in line with suggestions from consultation and the scoping workshop

Section	Consultee/ Commentator	Comments [sic]	Action
		"The most challenging part of taking part in the pre-type 1 diabetes/screening for us was discovering that one of our children was at stage 2. The upside of knowing this information, is that with the monitoring provided by the Elsa/Innodia teams, we are better able to understand how our daughters condition is progressing, and we are able to help my daughter to come to terms with her condition." ***"My daughter was diagnosed with T1d only after going into diabetic keto acidosis. She was one at the time and it was the most difficult thing as a parent to watch your child go through the trauma of a difficult T1d transition. Having the knowledge that my son will be fully T1d is huge in the sense that I can prepare for it. More importantly I can prepare him for it."*** And quality of life benefits: ***"My daughter is currently 10 years old. She has one more year at primary school and will then be transitioning to high school. She will be facing a lot of changes in her life and I think if we could delay the onset of Type 1 diabetes until she is a bit older, she will be more emotionally mature to deal with the situation".*** ***"Jude is currently 8, if we could delay the onset of T1d even by a year it would allow us to prepare him better for it and as he gets older he becomes more mature meaning he can manage it more responsible himself. Being the primary caregiver for a toddler with T1, a day without having to worry about insulin is a godsend, so having a few years would be amazing".***	

Section	Consultee/ Commentator	Comments [sic]	Action
		"If a treatment was made available to delay type 1 in my child it would allow her to get through some of her teen years which are already challenging enough without the burden of type 1. Also having better controlled blood glucose levels without the need for insulin for longer".	
	Juvenile Diabetes Research Foundation (JDRF)	Whilst the outcomes listed are appropriate, JDRF thinks that the time until diagnosis of stage 3 diabetes should be included as well.	Thank you for your comment. The outcomes section has been updated in line with suggestions from consultation and the scoping workshop
Equality	Sanofi (company)	NICE has previously stated that socioeconomic inequalities in the management of Stage 3 T1D require further consideration (21-23). Among people with Stage 3 T1D, low socioeconomic status (SES) is frequently associated with poorer disease management and outcomes (acute and long-term complications including higher DKA at diagnosis in paediatric patients, as well as mortality; 24-26) compared to higher SES. People with Stage 3 T1D and lower SES tend to have lower participation in structured diabetes education (27) and reduced attendance at specialist diabetes services than people with higher SES (28). In an interview, individuals with Stage 3 T1D and low SES in the UK highlighted that work commitments are a common barrier to attending specialist services and structured education, both of which are associated with improved outcomes in Stage 3 T1D (28). It is expected that delaying the onset of symptomatic Stage 3 T1D among people with Stage 2 T1D would provide valuable additional time for individuals of low SES to prepare for diabetes management (including attending structured education and specialist services) with more flexibility; delaying the onset of T1D symptoms also extends the window of time for	Thank you for your comment. If relevant, issues related to socioeconomic status may be considered by the committee during the appraisal; this is noted in the equality impact assessment (EIA).

Section	Consultee/ Commentator	Comments [sic]	Action
		physicians to engage with these patients and establish support systems before the urgencies of managing hyperglycaemia set in.	
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	Concerns here – a prerequisite of giving this therapy is knowledge of an individual with early-stage type 1 diabetes. This is usually only known with the introduction of screening (although some children may be identified clinically). Whilst there are some research screening programmes in the UK, none identify children/adults who have been identified through a universal screening approach from the general population; general population children/adults in the UK have mostly identified through social media and self-referral and are a self-selected group. FDRs have been identified through specific research programmes invited FDRs for antibody testing e.g. BOX, Innodia. If teplizumab is approved, it therefore excludes individuals who would have benefitted had universal screening been available, and this is expected to include those from marginalised groups.	Thank you for your comment. If relevant, equality issues related to screening may be considered by the committee during the appraisal; this is noted in the equality impact assessment (EIA).
	Diabetes UK	Teplizumab may be of particular benefit to individuals from disadvantaged backgrounds, those with mental health problems or other reason for finding engaging with the substantial challenges of insulin therapy difficult. For these individuals, it will provide near-normal glycaemic control for several years longer than they could achieve with no need for compliance beyond the 12-14 day period of teplizumab therapy. There will also be substantially reduced burden on carers especially for children for the period of delayed need for insulin. Individuals living with diabetes report “diabetes distress”, which includes the fear of hypo- or hyperglycaemia which may not be captured in assessments	Thank you for your comment. If relevant, issues related to socioeconomic status and people with a mental health condition may be considered by the committee during the appraisal; this is noted in the equality

Section	Consultee/ Commentator	Comments [sic]	Action
		of limitations of activities in every day life. Validated diabetes distress assessment tools exist. Children from families with low income / no car and one parent families may find to harder to access treatment due to travel and time involved accessing a specialised hospital setting. Consideration will need to be given to how to deliver the treatment in a safe and most cost effective way without exacerbating health inequalities.	impact assessment (EIA)
Other considerations	Association of British Clinical Diabetologists	As the treatment target individuals at risk of developing type 1 diabetes, education to primary and secondary staff on counselling skills to family, discussion on risk benefits etc needs to be also be considered. Is there a 'green' costs analysis – insulin pens / vials / disposables vs teplizumab?	Thank you for your comment. Education has been included as part of the comparator section. Green costs analysis is not included in the appraisal process.
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	To decide whether general population screening AND follow up of antibody positive individuals should be included in the cost evaluation. Note, to identify individuals in stage 2, screening should be offered – when this happens 80% will be in stage 1, and around 10-15% in stage 2, so there needs to be an ongoing follow up pathway and continuous case finding for stage 2 individuals (who progress from stage 1) as well as monitoring and support for stage 1 and 2. Research from the US (TrialNet) and Scandinavia (TEDDY) suggest that there is high dropout in screen positive children (50%) – if an adequate follow	Thank you for your comment. Pancreatic islet autoantibodies are required to be diagnosed with stage 2 type 1 diabetes and are not regularly tested for. Therefore, testing costs for pancreatic islet autoantibodies should

Section	Consultee/ Commentator	Comments [sic]	Action
		up pathway is not introduced to mitigate this, then potential recipients of teplizumab therapy will no longer be available to be identified for treatment.	be included in the economic analysis.
	Diabetes UK	Agree that the economic modelling should include the costs associated with screening. Recommend again that a separate analysis is considered for children 8-18 years.	Thank you for your comment. If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.
	Juvenile Diabetes Research Foundation (JDRF)	We question why there is no scoping workshop for this consultation. There are a number of factors that we think still need to be discussed, such as information provided to families about the stages of type 1, workforce capacity and planning, and care pathways in relation to Teplizumab. We would welcome a scoping workshop to discuss these factors.	Thank you for your comment. A scoping workshop was conducted, and responses have been included in the scope
Questions for consultation	Sanofi (company)	**Are there any interventions used for delaying type 1 diabetes in people at risk of developing the disease?** No, there are currently none. In addition, there are no disease modifying treatments to delay Stage 3 T1D in people with Stage 2 disease. **Are there any diagnostic tests required before teplizumab can be administered?**	Thank you for your comment. The scope has been updated in line with suggestions from consultation and the scoping workshop

Section	Consultee/ Commentator	Comments [sic]	Action
		There are no diagnostic tests required before administration of teplizumab in people with Stage 2 T1D. **Where do you consider teplizumab will fit into the existing care pathway for type-1 diabetes?** Teplizumab is anticipated to be available to all people over the age of 8 years with Stage 2 T1D. Based on clinical advice there is currently no established care pathway for these patients in the UK. However, clinical advice to Sanofi indicates that initially teplizumab is expected to be prescribed in specialist care with routine follow-up in secondary care (Option D) when "routine follow-up" is defined as the subsequent routine monitoring of Stage 2 T1D until progression to Stage 3 T1D. If "routine follow-up" is defined as the immediate monitoring of patients following administration for patient safety purposes, this would be expected to be in the same setting as treatment administration. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** There is no established standard of care for people with Stage 2 T1D, as outlined above. Clinical advice indicates the care usually involves education and monitoring and is delivered in secondary care. **Would teplizumab be a candidate for managed access?** We feel teplizumab is likely suitable for routine commissioning for all eligible patients. Sanofi are committed to bringing teplizumab to patients and are open to conversations regarding managed access if required. **Do you consider that the use of teplizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** We expect there are several benefits that are unlikely to be included in the	

Section	Consultee/ Commentator	Comments [sic]	Action
		QALY, as no data quantifying these impacts are available. These are however of high relevance to patients, caregivers and the broader healthcare system and include: • Increased time for patients to prepare for the onset and management of symptomatic Stage 3 T1D • Improving long-term outcomes in people with lower SES • Full impact on the caregiver • Impact on education and employment	
	Association of British Clinical Diabetologists	**Are there any diagnostic tests required before teplizumab can be administered?** Yes. T1D related autoantibody and metabolic testing is required to identify the target population. **Where do you consider teplizumab will fit into the existing care pathway for type-1 diabetes?** Teplizumab has a clear place in prevention, and before the existing and available care pathway for T1D. **Please select from the following, will teplizumab be:** A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care XXX D. Other (please give details):	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **Would teplizumab be a candidate for managed access?** Yes this would potentially be an early route into the UK NHS system to obtain data to support further rollout and use **Do you consider that the use of teplizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No	
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	1)There are no current interventions used to delay type 1 diabetes. 2)NEJM (Herold 2019) paper suggests there may be groups who respond better than others (but likely underpowered for this). 3)Children may have greater benefits by reducing exposure to hyperglycaemia (see above) 4)Diagnostic tests needs clarity i. presence of 2 or more islet autoantibodies measured on 2 occasions (Phillip Diab Care 2024 – international consensus JDRF International) ii. definition of dysglycaemia – can this be on HbA1c or only OGTT – implications of cost differences of both 5)Teplizumab will be delivered in secondary care and follow up in secondary care.	Thank you for your comment. The scope has been updated in line with suggestions from consultation and the scoping workshop

Section	Consultee/ Commentator	Comments [sic]	Action
		6) There is no existing care pathway for type 1 diabetes for teplizumab to fit into. For the introduction of teplizumab, there will need to be not only an NHS screening programme but also a follow up care pathway (see explanation above). Screening with the identification of antibody positive children is expected to result in a 60% expansion in clinical services (Ziegler Lancet 2024) – which may be offset by some of the costs in preventing hospitalisations, ketoacidosis, and psychological morbidity, and potentially reducing the risk of long-term complications mediated through reduction in DKA (although evidence is mixed on this).	
	Diabetes UK	Are there any subgroups of people in whom teplizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Children 8-18 years. Not more clinically effective, but likely more cost effective – see above. Teplizumab delays the age at which significant hyperglycaemia begins. There are some relevant studies e.g. Ramos et al which looked at children and young people 8-17 years. Are there any diagnostic tests required before teplizumab can be administered? Yes – testing for islet autoantibodies, and a glucose tolerance test. Where do you consider teplizumab will fit into the existing care pathway for type-1 diabetes? Teplizumab will extend the current pathway into actively managing the preclinical stages of type 1 diabetes. This would probably begin with screening of first degree relatives or patients currently in secondary care	Thank you for your comment. The scope has been updated in line with suggestions from consultation and the scoping workshop.

Section	Consultee/ Commentator	Comments [sic]	Action
		clinics for relatives with multiple islet autoantibodies (around 1 in 30 will be positive), and follow-up of positive cases and treatment when they enter "stage 2" (dysglycaemic) pre-clinical diabetes. Note that screening in itself has benefits in terms of reducing acute illness at diagnosis, DKA and the need for hospitalisation. Please select from the following, will teplizumab be: A. Prescribed in primary care with routine follow-up in primary care NO B. Prescribed in secondary care with routine follow-up in primary care NO C. Prescribed in secondary care with routine follow-up in secondary care **YES** D. Other (please give details): We asked ELSA study parents what the most convenient setting to administer the treatment would be. Parents all said a clinical environment close to home is preferred but were willing to make longer journeys for the benefits it could bring: ***"Obviously the nearer to home the better, in terms of convenience, but I would be prepared to travel for up to 3 hours from home."*** ***"It was my understanding that it has to be administered over 14 consecutive days. I would prefer it was administered in a hospital or clinical environment. As for travel, I would take my son to Timbuktu. Distance is not an issue."*** ***"The most convenient method would be orally in a hospital setting and I would be willing to travel anywhere in the U.K. for the treatment for my child."***	

Section	Consultee/ Commentator	Comments [sic]	Action
		One parent, a single mother of two, mentioned how much of a challenge travelling for treatment can be: ***"It's difficult for us because I am a solo mother who works and I have 2 kids and no other family nearby, so getting anywhere with one child is difficult without getting my other kid to miss school or be looked after by a friend."*** However, ultimately the same parent still expressed the same commitment to overcoming challenges: ***"It may imply some logistical difficulties but both my child and myself would be very keen to have the opportunity"*** <u>For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.</u> NO, but see below for some aspects of follow up. Clinically certainly to begin with as the therapy is administered using an IV administration and not yet widely used so should be administered in the safety of having access to emergency resources. Also it fits here as the intervention is for type 1 diabetes which is mostly managed in secondary care. 99.5% of people in the Ramos study experienced an adverse event, mainly associated with the administration of teplizumab (note - it was 97.3 for the placebo arm) - suggesting IV needs to be given in secondary care setting – as it was in the trial).	

Section	Consultee/ Commentator	Comments [sic]	Action
		Services would potentially need time to establish the service as this would require new service set up. Managed access could potentially help with new service set up? It is possible follow up screening e.g. Hba1c measurements and open access for any diabetes symptoms could be managed in primary care as they would be used to making the onward diabetes team referrals. GPs would need to be consulted about this however. <u>Do you consider that the use of teplizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?</u> YES, it will be of particular benefit to individuals from disadvantage backgrounds, mental health issues or other reason for finding engaging with the substantial challenges of insulin therapy difficult. For these individuals, it would provide near-normal glycaemic control for several years longer than they could achieve with no need for compliance beyond the 12-14 day period of teplizumab therapy. There will also be substantially reduced burden on carers especially for children for the period of delayed need for insulin. Individuals living with diabetes report “diabetes distress”, which includes the fear of hypo- or hyperglycaemia which may not be captures in assessments of limitations of activities of every day life. Validated diabetes distress assessment tools exist. (See references below on diabetes distress). QALY calculation should also factor in the cost of delayed / averted complications. Should be compared to pump / HCL therapy as well as MDI.	

Section	Consultee/ Commentator	Comments [sic]	Action
	Juvenile Diabetes Research Foundation (JDRF)	Diagnostic tests: an autoantibody test to detect the early stages of type 1 diabetes to ascertain suitability for this drug. Existing care pathway: JDRF believes the care pathway should be a combination of B and C. Prescribed in secondary care, with routine follow up in primary care, until stage 3, when the patient should be seen by secondary care clinicians. Substantial health-related benefits: Teplizumab can delay the onset of stage 3 type 1 diabetes by an average of three years. There are many benefits to delaying the onset. For children in the early stage of type 1 who are approaching adolescence, delaying type 1 would enable the pancreas to grow to adult size, giving better disease outcomes. Any time period that a person does not have to be dependent on insulin means they are avoiding important risks such as hypoglycaemia and the significant constant burdens of life with type 1. This can also play a key role in preventing complications such as eye, kidney, and heart diseases. Teplizumab can also help prevent traumatic and potentially fatal diabetic ketoacidosis (DKA) in individuals in the early stage of type 1. DKA is a severe lack of insulin which leaves the body unable to use glucose for energy. As a result, it starts to use fat instead, releasing chemicals called ketones which turn the blood acidic. Currently, one in four children in the UK experience DKA when diagnosed.	Thank you for your comment. No action required.
Additional comments on the draft scope	Sanofi (company)	**Title** The current title of this appraisal is out of line with the FDA approved indication (1) and clinical trial inclusion criteria (2). We suggest this is changed to “Teplizumab for delaying the onset of Stage 3 Type 1 diabetes	Thank you for your comment. The title has been updated in line with suggestions from

Section	Consultee/ Commentator	Comments [sic]	Action
		(T1D) in adults and paediatric patients aged 8 years and older with Stage 2 T1D [ID6259]". **Economic Analysis** We feel the inclusion of "the costs associated with diagnostic testing for diabetes antibodies in people with type 1 diabetes who would not otherwise have been tested" in the economic modelling is a consequence of an incorrectly defined patient population and as such should be removed. Stage 2 T1D is diagnosed through the presence of T1D antibodies and dysglycaemia (3-5) and these patients do not require any additional diagnostic tests to use teplizumab (29). **Scoping Workshop** We understand that in line with the NICE health technology evaluation manual scoping workshops are held "where the topic covers a new disease area or care pathway that NICE has not evaluated before or recently, or there are uncertainties about the evaluation that a workshop could address" (30). We believe that, for the reasons detailed in our response, the teplizumab appraisal meets all these criteria and are concerned that a scoping workshop has not been planned. We are specifically concerned because: • If licensed, teplizumab will be the first disease-modifying immunotherapy treatment for Stage 2 T1D. • The population defined is entirely disparate from the patient population in the FDA approved indication (1) and clinical trial inclusion criteria (2) • This is the first product for the delay of Stage 3 T1D in people with Stage 2 T1D and therefore there are uncertainties in the current care pathway.	consultation and the scoping workshop. Pancreatic islet autoantibodies are required to be diagnosed with stage 2 type 1 diabetes and are not regularly screened for. Therefore, screening costs for pancreatic islet autoantibodies should be included in the economic analysis. A scoping workshop was conducted and responses are included in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		• The economic analysis includes diagnostic testing, however there is no diagnostic tests required for the use of teplizumab in people with Stage 2 T1D. • The comparator defined as “no prophylaxis” suggests that teplizumab is incorrectly considered as a prophylactic treatment when it is disease-modifying. • Some of the outcomes proposed are not appropriate for the patients in whom teplizumab is anticipated to be indicated.	
	British Society For Paediatric Endocrinology And Diabetes (BSPED)	We do not consider a managed access programme equitable for the above reasons.	Thank you for your comment. No action required.
	Diabetes UK	Teplizumab will extend the current pathway into actively managing the preclinical stages of type 1 diabetes. This could probably begin with screening of first degree relatives or patients currently in secondary care clinics for relatives with multiple islet autoantibodies (around 1 in 30 will be positive), follow-up of positive cases and treatment when they enter “stage 2” (dysglycaemic) pre-clinical diabetes. Note that screening in itself has benefits in terms of reducing acute illness as diagnoses, DKA and the need for hospitalisation. This will only address around 10% of all the new cases, as 85-90% of new cases do not have a first degree relative. Ultimately, population screening would be required for more complete case finding.	Thank you for your comment. The scope is intended to provide a brief overview of the topic. Recommendations for research are not usually included. No action required

Section	Consultee/ Commentator	Comments [sic]	Action
		Scope should include recommendations for further research. (Possible areas could be the safety and effectiveness of using Teplizumab in under 8 years. And also in diverse populations including those of Asian and Black ethnicity).	
	Juvenile Diabetes Research Foundation (JDRF)	Under the Economic Analysis section, in the final paragraph, the sentence about economic modelling needs rephrasing to “people in the early stages of type 1 diabetes” instead of “people with type 1 diabetes”.	Thank you for your comment. The economic analysis section of the scope has been updated.